IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant(s): Walke *et al.*	Group Art Unit: 1647
Application No.: 09/893,321	Examiner: R. S. Landsman
Filed: 06/27/01	
Title: Polynucleotides Encoding Human GABA Receptors (As Amended)	Attorney Docket No.: LEX-0195-USA

APPEAL BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

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APPEAL BRIEF

Sir:

Appellants hereby submit an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Final Office Action mailed on October 18, 2003. The Notice of Appeal was timely submitted on December 16, 2003, and was received in the Patent and Trademark Office ("the Office") on December 22, 2003. This Appeal Brief is timely submitted in light of the concurrently filed Petition for an Extension of Time of four months to and including June 22, 2004 and authorization to deduct the fee as required under 37 C.F.R. § 1.17(a)(2) from Appellants' Representatives' deposit account. The Commissioner is also authorized to charge the fee for filing this Appeal Brief (**$165.00**), as required under 37 C.F.R. § 1.17(c), to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

Appellants believe no fees in addition to the fee for filing the Appeal Brief and the fee for the extension of time are due in connection with this Appeal Brief. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason related to this communication, the Commissioner is authorized to charge any underpayment or credit any overpayment to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

I. REAL PARTY IN INTEREST

The real party in interest is the Assignee, Lexicon Genetics Incorporated, 8800 Technology Forest Place, The Woodlands, Texas, 77381.

II. RELATED APPEALS AND INTERFERENCES

Appellants know of no related appeals or interferences.

III. STATUS OF THE CLAIMS

The present application was filed on June 27, 2001, claiming the benefit of U.S. Provisional

Application Numbers 60/214,083, which was filed on June 27, 2000 and included original claims 1-4. A Restriction and Election Requirement was issued by the Office on September 3, 2002, separating the original claims into two separate and distinct inventions. **In Appellants' Response to the Restriction and Election Requirement**, mailed on October 2, 2002, Appellants elected with traverse the claims of the Group I invention (comprising original claims 1 in part, 2 and 3) for prosecution on the merits. Appellants further elected, pursuant to 35 U.S.C. § 112, the species of SEQ ID NO:1 for initial examination on merits. A First Official Action, was issued on March 10, 2003,in which, as a result of Appellants' arguments, claims 1-4 were rejoined and were **rejected under 35 U.S.C. § 101, as allegedly lacking patentable utility. Claims 1-4 were also rejected under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility. Claims 3 and 4 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement and inadequate written description.** Additionally, Claim 2 was rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite, and claims 3 and 4 were rejected under 35 U.S.C. § 102(b) for being allegedly anticipated by others. In Appellants Response to the First Official Action, submitted to the Office on July 10, 2003, Appellants amended the title and claims 2-4 to further improve clarity, and added new claims 5 and 6 to more particularly point out and distinctly claim the invention. A Second and Final Official Action, was issued on August 18, 2003, in which rejection of all claims was maintained under 35 U.S.C. § 101 and § 112, first paragraph. Rejection of claims 3 and 4 under 35 U.S.C. § 112, **first paragraph, for lack of enablement and written description** was also maintained. While the rejection of claim 2 under 35 U.S.C. § 112, second paragraph was withdrawn, as was the rejection of claims 3 and 4 under 35 U.S.C. § 102(b). In Appellants Response to the Final Official Action, submitted on December 16, 2003, Appellants traversed the pending rejection of claims 1-6 under 35 U.S.C. § 101 and § 112, first paragraph. Appellants again amended the title, claims1, 3 and 4 to more clearly claim the present invention. An Advisory Action was mailed on February 4, 2004 maintaining the rejection of all claims under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as well as maintaining the rejection of claims 3 and 4 under 35 U.S.C. § 112, first paragraph, for lack of enablement and inadequate written description. Therefore, claims 1-6 are the subject of this appeal. A copy of the appealed claims are included below in the Appendix (**Section IX**).

IV. STATUS OF THE AMENDMENTS

Appellants believe there are no outstanding Amendments pending in this.

V. SUMMARY OF THE INVENTION

The present invention relates to Appellants' discovery and identification of novel human polynucleotide and amino acid sequences that encode human GABA receptor proteins (specification title, and at or about page 1, lines 26-28, page 2, lines 4-5, page 16, lines 7-13). GABA receptor proteins are a class of molecules with well-established function and utility having been implicated in mediating human mental disorders and diseases (specification ator about page 18, line 24) such as, *inter alia*, depression (specification at or about page 12, line 25). The sequences encoding the GABA receptor proteins of the present invention were shown to be expressed in human brain, pituitary, cerebellum, lymph node, adipose, esophagus, cervix, rectum, pericardium, and hypothalamus cells (specification at or about page 3, lines 22-24) and it is well-established and recognized by those of skill in the art that GABA receptors bind potent inhibitory neurotransmitters and this interaction serves as a target for a variety of pharmaceutically active agents such as benzodiazepines, barbiturates, and alcohol (specification at or about page 1, lines 26-28) and "because of their medical relevance, GABA receptors have been subject to considerable scientific scrutiny as shown in U.S. Application No. 09/183,253 (corresponding to WO9942580A2), herein incorporated by reference, which describes a variety of uses, assays, and applications" (specification at or about page 16, lines 9-13). Thus the sequences of the present invention encode a molecule with specific, substantial and well-established function and utility. Additional uses described in the specification include assessing temporal and tissue specific gene expression patterns (specification at or about page 6, line 20), particularly using a high throughput "chip" format (specification at or about page 5, line 26 through page 8), mapping the sequences to a specific region of a human chromosome and identifying protein encoding regions (specification at or about page 2, line 29-30), determining the genomic structure (specification at or about page 11, line 2), identifying verified intron/exon splice junctions (specification at or about page 11, lines 3-8) and in diagnostic assays (specification at or about page 18, line 20-21).

VI. ISSUES ON APPEAL

1. Do claims 1-6 lack a patentable utility?
2. Are claims 1-6 unusable by a skilled artisan due to a lack of patentable utility?
3. Are Claims 3 and 4 Enabled?
4. Do Claims 3 and 4 Meet The Written Description Requirement?

VII. GROUPING OF THE CLAIMS

For the purposes of the outstanding rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, the claims will stand or fall together. The rejection of claims 3 and 4 under 35 U.S.C. § 112, first paragraph for allegedly lacking enablement and lack of written description will stand and fall alone.

VIII. ARGUMENT

A. Do Claims 1-6 Lack a Patentable Utility?

The Final Action rejects claims 1-6 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by either a specific and substantial utility or a well-established utility. Appellants strongly disagree.

Appellants respectfully submit that the question of utility is a straightforward one as established by the courts. As set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group*

Inc., 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to

> prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (C.C.P.A. 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

> Even under the newly installed utility guidelines, Appellants note that MPEP 2107 (II)(B)(1) states:
> (1) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. (MPEP 2107 (II)(B)(1))

The Advisory Action reiterates the Examiner's persistent and erroneous position that Appellants did not disclose a specific or substantial function for the protein encoded by the sequences of the present invention. Appellants find this position to be without support.

Appellants have clearly asserted that the presently claimed sequences encode novel human GABA receptor proteins which have well-established function and utility. This assertion is clearly stated in the title of the application, regardless of its iteration, "NOVEL HUMAN GABA RECEPTORS AND POLYNUCLEOTIDES ENCODING THE SAME" (original) "HUMAN GABA RECEPTORS AND POLYNUCLEOTIDES ENCODING THE SAME" (as amended in response to the First Office Action) and as "POLYNUCLEOTIDES ENCODING HUMAN GABA RECEPTORS" (as amended in response

to the Final Office Action). In fact, in spite of twice objecting to the title, in the First and the Final Office Action, (for the use of the term novel and referral to an unclaimed (but disclosed) protein) not once did the Examiner challenge Appellants' assertion in the title that the sequences of the present invention encoded human GABA receptor proteins. Thus, one must reasonably assume that the Examiner accepted this assertion of identity and all that it implies as credible.

Additionally, in the specification as filed the novel human proteins encoded by the sequences of the present invention are said to be similar to human and other mammalian GABA receptors proteins (specification at page 2, lines 4-5) and are also said to "share structural similarity with GABA receptor proteins, and particularly GABA A receptor gamma-1, -2, and -3, -4, -5, and -6 subunits" (specification at page 16, lines 7-9). Furthermore, the assertion that the sequences of the present invention encode GABA receptor proteins is also made when the specification discloses the well-established specific and substantial function and physiologic roles of GABA receptor proteins, which are well known to the art (specification in page 1, lines 26-28). Those of skill in the art recognize the relationship between structure and function. GABA receptor proteins and their biological function are well known to those of skill in the art, as stated in the specification, see for example the statement in the specification (at page 16 on lines 9-13) that "Because of their medical relevance, GABA receptor proteins have been subject to considerable scientific scrutiny as shown in U.S. Application No. 09/183,253 (corresponding to WO9942580A2), herein incorporated by reference, which describes a variety of uses, assays, and applications". Additionally, the biologic function of GABA receptor proteins was described in the specification on page 1, at lines 26 -28, "GABA receptors bind potent inhibitory neurotransmitters and this interaction serves as a target for a variety of pharmaceutically active agents such as benzodiazepines, barbiturates, and alcohol". Thus, clearly Appellants asserted the sequences of the present invention encode human GABA receptor proteins and that the specific and substantial biologic role of GABA receptor proteins is <u>well-established</u> and recognized by those of skill in the art.

Further, Appellants invite the Boards' attention to the fact that, as submitted in Appellants' Response to the First Office Action is the fact that SEQ ID NO:2 shares greater than <u>99% identity</u> with a protein present in the world's leading scientific repository for biological sequence data (GenBank), and

has been annotated by third party scientists *wholly unaffiliated with Appellants* as "Gamma-aminobutyruc-acid receptor gamma-1 subunit precursor (GABA(A) (accession number Q8N1C3; alignment and GenBank report provided with Appellants' Response to the First Office Action as Exhibit D). Thus, clearly, when those of skill in the art were faced with identifying the product encoded by the sequences of the present invention, they readily recognized and concurred with Appellants assertion that they encode human GABA receptor proteins. Therefore, clearly Appellants' assertion regarding the identity and utility of the sequences of the present invention are credible to those of skill in the art.

Furthermore, as also submitted in Appellants' Response to the First Office Action was the following additional example of how well accepted the biological function and physiologic role of GABA receptor proteins are, Appellants quote the introduction of Chapter 16 of the sixth edition of the textbook Basic Neurochemisty: Molecular, Cellular and Medical Aspects, Editied by George J. Siegal, *et al.* (Lippincott, Williams & Wilkens).

> *"γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS). It was discovered in 1950 by Roberts and Awapara. Electrophysiological studies between 1950 and 1965 suggested a role for GABA as a neurotransmitter in the mammalian CNS. Since then, GABA has met the five classical criteria for assignment as a neurotransmitter: it is present in the nerve terminal, it is released from electrically stimulated neurons, there is a mechanism for terminating the action of the released neurotransmitter, its application to target neurons mimics the action of inhibitory nerve stimulation and specific receptors exist.*
>
> *In view of the ubiquitous nature of GABA in the CNS, it is perhaps not too surprising that its functional significance should be far-reaching. A growing body of evidence suggests a role for altered GABAergic function in neurological and psychiatric disorders of humans, including Huntington's disease, epilepsy, tardive dyskinesia, alcoholism, schizophrenia, sleep disorders, Parkinson's disease and mental retardation. Pharmacological manipulation of*

GABAergic transmission is an effective approach for the treatment of anxiety [1]. In addition, it has been demonstrated that the nervous system-depressant actions of barbiturates and other general anesthetics result from an enhancement of inhibitory synaptic transmission mediated by $GABA_A$ receptors [2,3]."

Textbooks are, by their very nature, representative of concepts generally accepted by those of skill in the art and thus clearly the specific and substantial function and utility of a novel human GABA receptor proteins is well-established and would be readily recognized by those of skill in the art, as among others, valuable drug targets for neurological disease.

I spite of this overwhelming evidence, the Examiner persists in arguing that because the specification as filed did not describe the protein encoded by the sequences of the present invention as the gamma-1 subunit precursor that no other assertions are of value and that this somehow indicates a lack of knowledge with regards to the protein. This is completely unfounded. The lack of Appellants' referral to the human GABA receptor protein as GABA receptor gamma-1 subunit precursor reflects only Appellants inability to presage a decision that would be made at a later date by others to refer to the novel GABA receptor protein encoded by the sequences of the present invention as human GABA receptor gamma-1 subunit precursor and nothing more.

In the First Office Action, the Examiner incorrectly stated that "it is clear from the instant specification that the claimed receptor is what is termed an "orphan receptor" (page 3, lines 11-12). In spite of Appellants identification of the sequences of the present invention as encoding novel human GABA receptor proteins. The Examiner's assumption appeared to be based in part of the finding that the sequences of the present invention share limited similarity to rat GABA(A) receptor gamma-1 subunit mRNA. This discrepancy probably results because, as Appellants have asserted, the sequences of the present invention encode human GABA receptor proteins, not those in the rat. Appellants then submitted the previously discussed evidence of the credibility of their assertion that the sequences of the present invention encode human GABA receptor proteins. In the form of an alignment that established that SEQ ID NO:2 shares greater than 99% identity with a protein present in the leading scientific repository for

biological sequence data (GenBank), and had been annotated by third party scientists *wholly unaffiliated with Appellants* as "Gamma-aminobutyruc-acid receptor gamma-1 subunit precursor (GABA(A) (accession number Q8N1C3; alignment and GenBank report provided with Appellants' Response to the First Office Action as Exhibit D). Thus, clearly, when those of skill in the art were faced with the task of identifying the product encoded by the sequences of the present invention, they also readily recognized and concurred with Appellants assertion that these sequences encode human GABA receptor proteins. Therefore, clearly Appellants' assertion regarding the identity and utility of the sequences of the present invention as well-established are credible to those of skill in the art.

Further evidence provided in support of Appellants' position regarding the biological function of the protein encoded by the sequences of the present invention is the result obtained using the Conserved Domain Architecture Retrieval Tool (CDART; provided in Appellants' Response to the First Office Action as Exhibit E). A CDART analysis of the protein sequences encoded by the present invention demonstrates that these sequences encode a neurotransmitter-gated ion-channel binding domain and a neurotransmitter-gated ion-channel transmembrane region. As GABA is a well-known and long established neurotransmitter, clearly this finding is consistent with Appellants' assertion that these sequences encode human GABA receptor proteins.

Still further evidence in support of Appellants' assertion that the utility of GABA receptor proteins is well-established and their biologic function well-known and long established is the three scientific review articles previously provided in Appellants' Response to the Final Office Action as Exhibit A. These three reviews demonstrate the well known role of GABA receptor proteins in human disease. The first is a recent review entitled "GABA, gamma-hydroxybuteric acid, and neurological disease" by Wong, Bottiglieri and Snead (Ann Neurol, 2003; 54 Suppl 6:S3-12). The second is a recent review entitled "GABAergic dysfunction in mood disorders" by Bambilla, *et al.*, (Mol Psychiatry, 2003 8(8):721-737) and the third is a review from 10 years ago entitled "Inherited disorders of GABA metabolism" by Jakobs, Jaeken and Gibson (J Inherit Metab Dis, 1993: 16(4):704-15).

While the Final Office Action recognizes that Appellants have asserted that the sequences of the present invention encode human GABA receptor proteins, it argues that as there is no data provided to

support this assertion it cannot be concluded that the sequences of the present invention encode GABA receptor proteins and therefore any arguments regarding the function of GABA receptor proteins are not applicable to the present case. The Final Action states (on page 3, lines 7-9 of the third paragraph) that "though Appellants suggest that the sequence(s) of the present invention encode GABA receptor proteins, this is speculative. There is no data to support this assertion." This emphasis is misplaced as it has long been established that "there is no statutory requirement for the disclosure of a specific example". *In re Gay*, 135 USPQ 311 (C.C.P.A. 1962). Appellants' assertion of the stated utility is legally sufficient and should control the utility analysis unless the Examiner meets the burden of establishing the lack of utility by making evidence of record that conclusively refutes the Appellants' asserted utility. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001). Thus, given the evidence previously presented by Appellants, the skilled artisan would readily appreciate the utilities asserted by Appellants' regarding the role of the proteins encoded by sequences of the present invention, including those associated with diseases that have been linked to the novel human GABA receptor proteins. Therefore, the present utility rejection must fail and should be overturned.

While the sequences of the present invention have been clearly shown to encode GABA receptor proteins, it is the Examiners' position that knowing a proteins structure is insufficient to identifying its function. Appellants disagree and strongly believe that the vast majority of those of skill accept the concept that there is a structure function relationship. In support of this position, as described in the First Office Action, the Examiner cited an article by Skolnick, *et al.* (Trends in Biotech *18*:34-39, 2000) for the proposition that "(k)nowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function" (Skolnick at page 36, emphasis added). However, Skolnick, *et al.* concerns predicting protein function not by overall amino acid homology to other family members, but instead concerns prediction of function based on the presence of certain functional "motifs" present within a given protein sequence. Thus, Skolnick does not apply to the

current situation, where overall protein homology is used to assign function to a particular sequence. However, even in the event that Skolnick is applicable, Skolnick itself concludes that "sequence-based approaches to protein-function prediction have proved to be very useful" (Skolnick at page 37), admitting that such methods have correctly assigned function in 50-70% of the cases, thus a majority of the time supporting rather than refuting Appellants assertions.

The Examiner next cited Bork (Genome Research *10*:398-400, 2000) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The Action directs attention to page 399, on which the author notes the limitations of various methods of analysis. It is of interest that in his "analysis" Bork often uses citations to many of his own previous publications, an interesting approach. ' My position is supported by my previous disclosures of my position.' If Bork's position is supported by others of skill in the art, one would expect that he would reference them rather than himself to provide support for his statements. Given that the standard with regard to obtaining U.S. patents is those of skill in the art, this observation casts doubt on the broad applicability of Bork's position. It should also be noted that in Table 1,on page 399, in which selected examples of prediction accuracy are presented, that the reported accuracy of the methods which Appellants have employed are, in fact, very high. While nowhere in Bork is there a comparison of the prediction accuracy based on the percentage homology between two proteins or two classes of proteins, " Homology (several methods)" is assigned an accuracy rate of 98% and "Functional features by homology" is assigned an accuracy rate of 90%. Given that these figures were obtained based on what is at least a 4 year old analysis, these high levels of accuracy would appear to support rather than refute Appellants assertions in the present case. Additionally Bork even states (on page 400, second column, line 17) that " However, there is still no doubt that sequence analysis is extremely powerful". In summary, it is clear that it is not Bork's intention to refute the value of sequence analysis but rather he is indicating that there is room for improvement .

The Examiner next cited Doerks *et al.* (Trends in Genetics *14*:248-250, 1998) in support that sequence-to-function methods of assigning protein function are prone to errors due to partial annotation, multifunctionality and over prediction. However, Doerks *et al.* states that "utilization of family information

and thus a more detailed characterization" should lead to "simplification of update procedures for the entire families if functional information becomes available for at least one member" (Doerks *et al.*, page 248, paragraph bridging columns 1 and 2, emphasis added). Appellants point out that GABA receptor proteins represent a very well-studied protein family with a large amount of known functional information, exactly the situation that Doerks *et al.* suggests will "simplify" and "avoid the pitfalls" of previous sequence-to-function methods of assigning protein function (Doerks *et al.*, page 248, columns 1 and 2). Thus, instead of supporting the Action's position against utility, Doerks *et al.* supports Appellants' position that the presently claimed sequences have a well-established utility.

The Examiner also cited Smith, *et al.* (Nature Biotechnology *15*:1222-1223, 1997) as teaching "that there are numerous cases in which proteins of very different functions are homologous" (Action at page 4). However, the Smith, *et al.* article also states "the major problems associated with nearly all of the current automated annotation approaches are - paradoxically - minor database annotation inconsistencies (and a few outright errors)" (page 1222, second column, first paragraph, emphasis added). Thus, Smith, *et al.* do not in fact seem to stand for the proposition that prediction of function based on homology is fraught with uncertainty, and thus also does not support the alleged lack of utility.

The Examiner next cited Brenner (Trends in Genetics *15*:132-133, 1999) as teaching that proposition that accurate inference of function from homology is a difficult problem . However, this statement is based on the assumption that "if there are only 1000 superfamilies in nature, then most homologs must have different molecular and cellular functions" (page 132, second column). Furthermore, Brenner suggests that one of the main problems in using homology to predict function is "an issue solvable by appropriate use of modern and accurate sequence comparison procedures" (page 132, second column), and in fact references an article by Altschul *et al.*, which is the basis for one of the "modern and accurate sequence comparison procedures" used by Appellants. Thus, the Brenner article also does not support the alleged lack of utility.

Finally, the Examiner cited Bork, *et al.* (Trends in Genetics *12*:425-427, 1996) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The question as to whether Bork's positions are generally supported by those of skill in the art was discussed

above in the paragraph regarding the other Bork citation. It should also be noted that this article was published approximately 6 years ago and thus refers to errors or "traps" associated with earlier algorithms and technologies in a field that has undergone constant improvement. This publication identifies (Table 1) various areas in which incorrect information appears in sequence databases. These "traps" include Synonyms - a single gene having a variety of names, Different gene-same name- when the same name is used to describe different genes, Spelling errors, Contamination-the unintentional inclusion of vector sequences, etc. and propagation of incorrect functional associations based on poorly analyzed homology. All of these issues can effect the accuracy of sequence base analysis, however all can be overcome by a more careful analysis as would be done by one of skill in the art. Automatic methods of sequence homology as identified by any algorithm is a staring point for consideration, and one of skill in the art can then through further analysis, structure-function analysis, etc. can and should then verify the associations. For example in addition to algorithm based sequence analysis the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (1 B.S. and 4 Ph.D. level scientists). Clearly such highly skilled and careful analysis reduces the influence of such "traps". Furthermore, in the final section of this publication (page 427) it again becomes cleat that Bork, *et al.* do not discount the value of sequence analysis "we wish to point out that sequence database are the most useful tool in sequence analysis and the question should be how can one further improve their value". Thus clearly this publication represents a call to action to enhance the already high value of sequence analysis rather than an indictment of the utility of sequence based analysis. Therefore, as Bork, *et al.* identifies the high value of sequence based analysis it actually supports rather than refutes Appellants assertions regarding the utility of the present invention.

Thus, a careful reading of the cited "relevant literature" does not in fact support the concept that function cannot be based on sequence and structural similarity, in contrast many of the examples actually support the use of such methodologies while identifying several areas in which caution should be exercised. As stated previously these inaccuracies and potential pitfalls can be overcome by a more careful analysis by those of skill in the art. Automatic methods of sequence homology identification was only the staring point for consideration the sequences of the present invention underwent careful analysis by a series of

individuals of skill in the art, many highly qualified (1 B.S. and 4 Ph.D. level scientists). These articles are just examples of the few contrarian articles that the PTO has repeatedly attempted to use to deny the utility of nucleic acid sequences based on a small number of publications that call into doubt prediction of protein function from homology information and the usefulness of bioinformatic predictions. While there may not be a 100% consensus within the scientific community regarding prediction of protein function from homology information this is not unusual, in the scientific community or the legal community, nor is it indicative of a general lack of consensus. A few rare exceptions do not a rule make.

Further evidence supporting the position that bioinformatic information is recognized to be of value by those of skill in the art is the result of a recent search of the NCBI-NLM-NIH public scientific database "PubMed" using the term "bioinformatics" which resulted in 5,548 different scientific publications (these are not currently provided to avoid unnecessarily burdening the USPTO's scanning group). If bioinformatic information is not a method accepted by those of skill in the art to predict protein function based on structural information, why would so many publications be reporting the results of its use? Clearly this suggests that the vast majority of those of skill in the art do recognize a structure-function relationship and view bioinformatic information as having value and utility.

Another form of evidence supporting the position that bioinformatic information is recognized to be of value by those of skill in the art is the fact that many scientists, corporations and institutions elect to allocate significant proportions of their limited resources for access to private bioinformatic systems and databases. Thus, it would appear obvious that the majority of those of skill in the art value such structural based analyses and accept the findings of bioinformatic analysis for they are willing to pay dearly for access to such information.

Still another and perhaps the most persuasive form of evidence supporting the position that bioinformatic information is recognized to be of value by those of skill in the art is the issuance of multiple U.S. patents regarding bioinformatic prediction and methods for doing the same (see for example, U.S. Patent Nos. 6,229,911, 6,466,874, 6,567,540, 6,615,141, 6,631,331, 6,651,008, 6,677,114, copies of issued U.S. Patents not provided pursuant to current United States Patent and Trademark Office policy). Of particular interest might be U.S. Patent No. 6,466,874, one of whose claims reads on "A

method of identifying proteins as functionally linked, the method comprising comparing sequences to find homologous functional domains." As issued U.S. patents are legally presumed to be valid, one must presume that the method of carrying out an analysis based on structure-function relationship has utility. One must logically, therefore, presume that both those of skill in the art recognize the utility of structural homology based bioinformatic prediction.

Appellants respectfully point out that, as discussed above, the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be believable. Appellants submit that the overwhelming majority of those of skill in the relevant art would believe prediction of protein function from homology information and the usefulness of bioinformatic predictions to be powerful and useful tools. Clearly the several forms of evidence presented, and certainly the issuance of U.S. Patents suggest that those of skill in the art recognize the utility of bioinformatic analysis and its credibility in assessing structure function relationships. Thus the vast majority of those of skill in the art would believe that Appellants sequences encode human GABA receptor proteins. When faced with identifying the function of sequences that are 99% identical at the amino acid level to those of the present invention, those of skill in the art identified these sequences as GABA receptor protein subunits. Appellants have asserted that the sequences of the present invention encode a GABA receptor proteins and in a prior responses provided evidence that those of skill in the art would clearly find this assertion credible. It is not the role of the Examiner to simply disregard third party scientific evidence that supports Appellants' assertions "as deemed non-persuasive". The burden is now on the Examiner to provide objective evidence that in fact the sequences of the present invention do not encode GABA receptor proteins or that GABA receptor proteins have no utility.

Furthermore, Appellants respectfully submit that the Examiner's position, in light of the evidence provided, runs contrary to Example 10 of the PTO's Revised Interim Utility Guidelines Training Materials (pages 53-55), which establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, is not proper when there is no reason to doubt the asserted utility of a full length sequence (such as the presently claimed sequence) that has a similarity score of 95% to a protein

having a known function. In the Analysis portion of Example 10 it states that "Based on applicant's disclosure and the results of the PTO search, there is no reason to doubt the assertion that SEQ ID NO:2 encodes a DNA ligase. Further DNA ligases have a well-established use in the molecular biology art based on this class of proteins ability to ligate DNA. .....Note that if there is a well-established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed..... Thus the conclusion reached from this analysis is that a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph, utility rejection should not be made."

In the present case, clearly evidence supports Appellants' assertions that the sequences of the present invention encode novel human GABA receptor proteins, a class of proteins for which there is a well established utility that is readily recognized by those of skill in the art. Thus, the present case is essentially identical to that presented in Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55). In the present case it is clear that the sequences of the present invention encode novel human GABA receptor proteins. However, the Examiner dismisses Appellants' continued assertions that the protein of the present invention is human GABA receptor proteins and that the function of GABA receptor proteins as a class of proteins are well known to those of skill in the the art (as demonstrated by the evidence provided). Thus, according to the guidelines the conclusion reached from this analysis is that a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph, utility rejection should not have been made. Thus the rejection of the presently claimed invention under a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph utility rejection should be overruled.

Clearly, given the evidence that the sequences of the present invention encode GABA receptor proteins, and given the well-established utilities described for GABA receptor proteins and the evidence provided that the claimed sequences provide a specific marker of the gene encoding GABA receptor proteins and as such provide a unique identifier of the corresponding gene in the human genome. Such specific markers are targets for discovering drugs that are associated with human mental disorders and diseases (specification at page 18, line 24) such as, *inter alia*, depression (specification at page 12, line 25). Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification

detailed.

Prior to use in such a process, the Examiner seems to want Appellants to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications that meet the requirements of § 101. Appellants respectfully point out that knowledge of the exact function or role of the presently claimed sequence is not required to track expression patterns using a DNA chip. As set forth in Appellants' First Response, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. Even though it is not a requirement for use of a sequence on a DNA chip, clearly, the claimed sequences are known to encode human GABA receptor proteins, a class of proteins whose function and utility is well-established and which are known to play a role in human disease. Thus these sequences provide a specific marker of the gene encoding this protein and provide a unique identifier of the corresponding gene in the human genome. Such specific markers are targets for discovering drugs that are used to mediate human mental disorders and diseases, such as depression. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing GABA receptor protein gene expression using, for example, DNA chips, as the specification details at least on or about page 5, line 26 through page 8. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776 (copies of issued U.S. Patents not provided pursuant to current United States Patent and Trademark Office policy).

Additionally, only a small percentage of the genome (2-4%) actually encodes exons, which in turn encode amino acid sequences. Thus, not all human genomic DNA sequences are useful in such gene chip applications. This further discounts the Examiner's position that such uses are "generic". The present claims clearly meet the requirements of 35 U.S.C. § 101. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Evidence of the "real world" substantial utility of the present invention is provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Agilent Technologies, Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value (net equity value of the transaction was $620 million) that it was acquired by large pharmaceutical company, Merck & Co., for significant sums of money. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. The sequences of the present invention describe novel gene encoding GABA receptor proteins and provide a unique identifier of the corresponding gene. Therefore, as the present sequences are specific markers of the human genome, and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such gene chips. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

An additional utility of the present invention is in expanding the utility of data coming from the human genome project. Persons of skill in the art, as well as thousands of venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. All current therapeutics used in humans directly or indirectly interact with biological sequences encoded by the human genome, and virtually all future human therapeutics shall do likewise. Consequently, billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success, as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and

the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

Although Appellants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotide, the present nucleotide sequence has a specific utility in mapping the protein encoding regions of the corresponding human chromosome, as detailed in the specification Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, as only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Appellants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Appellants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*supra at* pp. 1317-1321, including Fig. 11 at pp. 1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that encodes human GABA receptor proteins and thus

provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

As evidence of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided in Appellants' prior Response as Exhibit F. This is the result of a blast analysis using SEQ ID NO:1 of the present invention when overlaid upon the identified human genomic sequence. This result indicates that the sequence of the present invention is encoded by 11 different exons spread non-contiguously along a region of human chromosome 4 (4p12), which is represented by clones AC0095058 and AC096592. Thus clearly one would not simply be able to identify the protein encoding exons that make up the sequence of the present intention, nor to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what the specific sequences were. Additionally, it should be noted that the gene of Q8N1C3 (previously presented as Exhibit D), Gamma-aminobutyric-acid receptor gamma-1 subunit precursor (GABA(A)) receptor also maps to the same region of human chromosome 4. Thus further supporting Appellant's assertion that the sequences of the present invention encode a variant of the human GABA(A) receptor.

The Examiner's negates the use of the sequences of the present invention in both DNA chip analysis and gene mapping based apparently on the assumption that as theoretically any human nucleic acid sequence could be used in these methods, such a utility is not specific. This position may represent a confusion between the requirement for a specific utility, which is the proper standard for utility under 35 U.S.C. § 101, with a requirement for a unique utility. The relevant case law cited by Appellants makes it abundantly clear that the presence of other or even more useful polymorphic markers for forensic analysis does **not** mean that the present sequences lack a specific utility. As clearly stated by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991; "*Carl Zeiss*"):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a

lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Importantly, the holding in the *Carl Zeiss* case is mandatory legal authority that essentially controls the outcome of the present appeal. This case, and particularly the cited quote, directly rebuts any such argument. Furthermore, the requirement for a unique utility is clearly not the standard adopted by the Patent and Trademark Office. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer and bacterial or viral infections, just to name a few particular examples, because examples of each of these have already been described and patented. All batteries have the exact same utility - specifically, to provide power. All automobile tires have the exact same utility - specifically, for use on automobiles. All golf balls and golf clubs have the exact same utility - specifically, use in the game of golf. All cancer treatments have the exact same utility - specifically, to treat cancer. All anti-infectious agents have the exact same broader utility - specifically, to treat infections. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequences, which encode human GABA receptor proteins, clearly meet the requirements of 35 U.S.C. § 101.

The Board is further requested to consider that, given the huge expense of the drug discovery process, even negative information has great "real world" practical utility. Knowing that a given gene is not expressed in medically relevant tissue provides an informative finding of great value to industry by allowing for the more efficient deployment of expensive drug discovery resources. Such practical considerations are equally applicable to the scientific community in general, in that time and resources are not wasted chasing what are essentially scientific dead-ends (from the perspective of medical relevance). Clearly, compositions that enhance the utility of such DNA gene chips, such as the presently claimed sequences encoding GABA receptor proteins, which Appellants have shown are well-established drug targets for

mental and behavioral disorders, among others, must in themselves be useful. Moreover, the presently described GABA receptor proteins provide uniquely specific sequence resources for identifying and quantifying full length transcripts that were encoded by the corresponding human genomic locus. Accordingly, there can be no question that the described sequences provide an exquisitely specific utility for analyzing gene expression.

Finally, with full recognition of the fact that all patent applications are examined on their own merits and that the prosecution of one patent does not effect the prosecution of another patent, *In re Wertheim,* 541 F.2d 257, 264, 191 USPQ 90, 97 (CCPA 1976), however the issue at hand in one of whether the fact that patents have issued recognizing the utility of a class of molecules does this confers a statutory precedent of patentability to a broad class of compositions. Thus, there remains a lingering issue regarding due process and equitable treatment under the law. While Appellants are well aware of the new Utility Guidelines set forth by the USPTO, Appellants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Appellants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (copies of issued U.S. Patents not provided pursuant to current United States Patent and Trademark Office policy), and recently issued U.S. Patent No. 6,340,583 (copies of issued U.S. Patents not provided pursuant to current United States Patent and Trademark Office policy), none of which contain examples of the "real-world" utilities that the Examiner appears to desire. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section IV, below), Appellants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While

Appellants agree that each application is examined on its own merits, Appellants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Appellants invention to a different standard of utility appears inconsistent and inequitable, such a judgement being arbitrary and capricious, a violation of due process and equal protection under the law and cannot be maintained.

Thus in summary, Appellants submit that the presently claimed molecules have been shown to encode, as asserted in the specification as filed, GABA receptor proteins, whose utility and biological function is well-established. Thus, the present situation directly tracks Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55), which establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, is not proper when a full length sequence (such as the presently claimed sequence), and has a similarity score greater than 95% to a protein having a known function (such as the greater than 99% identity between the presently claimed sequences and those of the cited GABA receptor of Q8N1C3). Furthermore this brief has described a series of additional substantial, specific, credible and well-established utilities for the present invention. Therefore, Appellants submit that as the presently claimed sequence molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of the claims under 35 U.S.C. § 101 and under 35 U.S.C. § 112, first paragraph is not proper. Thus, Appellants respectfully request that the rejection be overturned.

B. Are Claims 1-6 Unusable Due to a Lack of Patentable Utility?

The Final Office Action next rejects claims 1-6 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility.

The arguments detailed above in **Section VIII(A)** concerning the utility of the presently claimed sequences are incorporated herein by reference. As the Federal Circuit and its predecessor have

determined that the utility requirement of Section 101 and the how to use requirement of Section 112, first paragraph, have the same basis, specifically the disclosure of a credible utility (*In re Brana, supra*; *In re Jolles*, 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche*, 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971)), Appellants submit that as claims 1-4, 11 and 12 have been shown to have "a specific, substantial, and credible utility", as detailed in **Section VIII(A)** above, the present rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph, cannot stand. Therefore, Appellants submit that the rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph, must be overruled.

C. Are Claims 3 and 4 Enabled?

The Final Office Action next rejected claims 3 and 4 under 35 U.S.C. § 112, first paragraph, as allegedly not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Appellants respectfully maintain their traverse.

Appellants respectfully submit that the Examiner has failed to present reasoning sufficient to establish a *prima facie* case supporting the present § 112 rejection, and accordingly the rejection is improper because: the Examiner's comments were not relevant to the established legal standard of enablement; the Examiner's failure to attribute adequate weight and attention to the detailed level of teaching clearly provided in the specification; and the reasoning for the enablement rejection provided by the Examiner failed to adequately consider the high level of technical knowledge that can be attributed to those skilled in the art in the field of the present invention.

In attempting to establish a *prima facie* case to support the § 112 rejection of the composition claims, the Final Office Action questions whether the claimed compositions are sufficiently enabled to allow those skilled in the art to practice aspects of the invention involving standard molecular biological techniques. The § 112 rejection, as applied against the nucleic acid compositions, is completely misplaced. It has long been established that composition claims are enabled by defining any practical use of the claimed compound. *In re Nelson*, 126 USPQ 242 (CCPA 1960); *Cross v. Iizuka*, *supra*. "The enablement requirement is met if the description enables any mode of making and using the invention." *Johns Hopkins*

Univ. v. CellPro, Inc., 47 USPQ2d 1705, 1719 (Fed. Cir. 1998), citing *Engel Indus., Inc. v. Lockformer Co.*, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991). Thus, the enablement issue should be resolved. Enablement only requires that the specification describe a practical use for the composition defined in the claims, and that a skilled artisan be able to make and use the claimed DNA segments without undue experimentation.

The Final Office Action seems to contend that the specification provides insufficient guidance regarding the biological function or activity of certain of the claimed compositions. However, such an enablement standard conflicts with established patent law and furthermore, in fact, the specification provides the clear assertion that the sequences of the present invention encode GABA receptor proteins. Those of skill in the art agree that the sequences of the present invention encode GABA receptor proteins and GABA receptor proteins are very well-known to those of skill in the art with well-established utilities including as drug targets. Thus information obtained using, for example, DNA chips would be extremely useful and would be readily recognized as such by those of skill in the art.

The Final Office Action argues essentially that though a first nucleic acid may share identical regions with a second nucleic acid, it is highly unpredictable as to whether the two nucleic acids encode proteins having identical functions. However, this argument is misplaced, first, because all species of an invention are not required to have the exact same function, and second, because numerous uses of the claimed sequences do not require knowledge of any functional aspects of the amino acid sequences. Appellants point out that significant commercial exploitation of nucleic acid sequences requires no more information than the nucleic acid sequence itself. Applications ranging from gene expression analysis or profiling (utilizing, for example, arrays of short, overlapping or non-overlapping, oligonucleotides and DNA chips, as described above) to chromosomal mapping (utilizing, for example, short oligonucleotide probes or full length DNA sequences, as described above) are practiced utilizing nucleic acid sequences and techniques that are well-known to those of skill in the art. The widespread commercial exploitation of nucleic acid sequence information points to the level of skill in the art, and the enablement provided by disclosures such as the present specification, which include specific nucleic acid sequences and guidance regarding the various uses of such sequences.

Even though the burden has been improperly shifted to Appellants, the following section is being provided to demonstrate that the specification is fully enabling in view of the detailed guidance and teaching provided in the specification within the context of the high level of technical knowledge present in the art regarding the use of nucleic acids such as those presently claimed.

The Final Office Action questions the teaching and guidance in the specification for certain aspects of the present invention. However, as discussed above, this requirement is completely misplaced. There is sufficient knowledge and technical skill in the art for a skilled artisan to be able to make and use the claimed DNA species in a number of different aspects of the invention entirely without further details in a patent specification. For example, it is not unreasonable to expect a Ph.D. level molecular biologist to be able to use the disclosed sequence to design oligonucleotide probes and primers and use them in, for example, PCR based screening and detection methods to obtain the described sequences and/or determine tissue expression patterns. Nevertheless, the present specification provides highly detailed descriptions of techniques that can be used to accomplish many different aspects of the claimed invention, including recombinant expression, site-specific mutagenesis, *in situ* hybridization, and large scale nucleic acid screening techniques, and properly incorporates by reference a montage of standard texts into the specification, such as Sambrook *et al.* (*Molecular Cloning, A Laboratory Manual*) and Ausubel *et al.* (*Current Protocols in Molecular Biology*) to provide even further guidance to the skilled artisan. Incorporation of material into the specification by reference is proper. *Ex parte Schwarze*, 151 USPQ 426 (PTO Bd. App. 1966). The § 112, first paragraph rejection is thus *prima facie* improper:

> As a matter of patent office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi & Horton, 169 USPQ 367, 369 (CCPA 1971), emphasis as in original. In any event, an alleged lack of express teaching is insufficient to support a first paragraph rejection where one of skill in the art would know how to perform techniques required to perform at least one aspect of the invention. As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re*

Wands, supra. In fact, it is preferable that what is well known in the art be omitted from the disclosure. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). As standard molecular biological techniques are routine in the art, such protocols do not need to described in detail in the specification.

Furthermore, a specification "need describe the invention only in such detail as to enable a person skilled in the most relevant art to make and use it." *In re Naquin*, 158 USPQ 317, 319 (CCPA 1968); emphasis added. The present claims are thus enabled as they are supported by a specification that provides sufficient description to enable the skilled person to make and use the invention as claimed.

As detailed in the sections above, all aspects of the enablement rejection under 35 U.S.C. § 112, first paragraph have been overcome, particularly as the specification provides the clear assertion that the sequences of the present invention encode GABA receptor proteins, those of skill in the art agree and GABA receptor proteins are very well-known to those of skill in the art with well-established utilities. Appellants therefore respectfully submit that this rejection should be overturned.

D. Do Claims 3 and 4 Lack Sufficient Written Description?

The Final Office Action next rejected claims 3 and 4 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Final Office Action stated that claim 3 fails to meet the written description requirement because it "does not require that the nucleic acid molecules possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature" (the Final Action at page 10).

The Final Office Action suggests that a stretch of at least 80 consecutive nucleotides of SEQ ID NO:1 or 3 is not a meaningful structural limitation and a distinguishing feature, because such a limitation does not require that the nucleic acid molecules possess any particular biological activity, nor any particular conserved structure, or other distinguishing feature (the Final Action at page 8). Appellants point out that **every aspect** of this argument fails to take into consideration the proper basis for compliance with the

written description requirement under 35 U.S.C. § 112, first paragraph. First, the Examiner seems to be requiring that the structural limitation of "at least 80 consecutive nucleotides of SEQ ID NO: 1 or 3" have a functional basis, specifically that it possess a "particular biological activity". This argument completely defies logic - of course this **structural** limitation does not have a functional basis. Second, the limitation of "at least 80 consecutive nucleotides of SEQ ID NO:1 or 3" does in fact have a particular conserved structure, specifically, each and every species is conserved within the nucleotide sequence of SEQ ID NO:1 or 3. Thus, these species are each unique markers of the nucleotide sequence of SEQ ID NO:1 or 3. Thus, the Examiner's argument in no way supports the allegation that claims 3 and 4 do not meet the written description requirement under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the invention. The Federal Circuit in *Vas-Cath Inc. v. Mahurkar* (19 USPQ2d 1111 (Fed. Cir. 1991); "*Vas-Cath*") held that an "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*." *Vas-Cath*, at 1117, emphasis in original. However, it is important to note that the above finding uses the terms reasonable clarity to those skilled in the art. Further, the Federal Circuit in *In re Gosteli* (10 USPQ2d 1614 (Fed. Cir. 1989); "*Gosteli*") held:

> Although [the applicant] does not have to describe exactly the subject matter claimed, . . . the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

Gosteli at 1618, emphasis added. Additionally, *Utter v. Hiraga* (6 USPQ2d 1709 (Fed. Cir. 1988); "*Utter*"), held "(a) specification may, within the meaning of 35 U.S.C. § 112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses" (*Utter*, at 1714). Therefore, all Appellants must do to comply with 35 U.S.C. § 112, first paragraph, is to convey the invention with reasonable clarity to the skilled artisan.

Further, the Federal Circuit has held that an adequate description of a chemical genus "requires a precise definition, such as by structure, formula, chemical name or physical properties" sufficient to distinguish the genus from other materials. *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993; "*Fiers*"). *Fiers* goes on to hold that the "application satisfies the written description requirement since it sets forth the . . . nucleotide sequence" (*Fiers* at 1607). In other words, provision of a structure and

formula - the nucleotide sequence - renders the application in compliance with 35 U.S.C. § 112, first paragraph.

More recently, the standard for complying with the written description requirement in claims involving chemical materials has been explicitly set forth by the Federal Circuit:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *Regents of Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to distinguish the genus from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. As further elaborated by the Federal Circuit in *Regents of Univ. of California v. Eli Lilly and Co.*:

> In claims to genetic material ... a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art cannot, as one can do with a fully described genus, visualize or recognize the identity of members of the genus. (Emphasis added)

Thus, as opposed to the situation set forth in *Regents of Univ. of California v. Eli Lilly and Co.* and *Fiers*, the nucleic acid sequences of the present invention are not distinguished on the basis of function, or a method of isolation, but in fact are distinguished by structural features - a chemical formula, *i.e.*, the *sequence itself.*

Using the nucleic acid sequences of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to **distinguish** the claimed nucleic acids from other materials on the basis of the specific **structural** description provided. Polynucleotides comprising at least 80 contiguous bases from SEQ ID NO: 1 or 3 are within the genus of the instant claims, while those that lack this structural feature lie outside the genus. The claimed genus of polynucleotides is clearly defined in structural terms, which is **all that is required** of claims 3 and 4 to meet the written description requirement of

35 U.S.C. § 112, first paragraph. Therefore, for each of the foregoing reasons, Appellants submit that the rejection of claims 3 and 4 under 35 U.S.C. § 112, first paragraph should be overturned.

IX. APPENDIX

The claims involved in this appeal are as follows:

1. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an amino acid sequence drawn from the group consisting of SEQ ID NOS: 2 and 4.

2. An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence of SEQ ID NO:2; and

(b) hybridizes under stringent conditions including washing in 0.1xSSC/0.1% SDS at 68°C to the complement of the nucleotide sequence of SEQ ID NO: 1.

3. An isolated nucleic acid molecule comprising at least 80 contiguous bases of nucleotide sequence of SEQ ID NO: 1.

4. An isolated nucleic acid molecule comprising at least 80 contiguous bases of nucleotide sequence of SEQ ID NO: 3.

5. An expression vector comprising a nucleic acid molecule of Claim 1.

6. A cell comprising the expression vector of Claim 5.

X. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 1-6 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility is unwarranted. Furthermore, Appellants further believe that the inventions of claims 3 and 4 are enabled and meet the written description requirement. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

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